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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,852	GAZIT, EHUD	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,40,72-79,81-102,118,141,148 and 155-159* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,72,74,77-79,81,95 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/07;7/10/08;8/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 40,73,75,76,82-94,96,98-102,118,141,148 and 155-159.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 8 August 2008 has been entered into the record and has been fully considered.

It is noted that Applicant's amendment of 12/30/05 had cancelled claims 41-73. However, claims 72 and 73 are still present with the "Original" status in the present amendment. This error was inadvertently overlooked in the last Office Action. Because Applicants elected claim 72 and its dependent claims in response to the restriction requirement, it is presumed that the above mentioned numbering is a typographical error. Applicants are required to submit a corrected claim sheet with the appropriate claim numbering with their response to this Office Action.

Election/Restrictions

2. Applicant's election of Group I, claims 1, 12, 71-101, in the reply filed on 8 August 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 40, 73, 75-76, 82-94, 96, 98-102, 118, 141, 148, 155-159 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being

drawn to a nonelected invention and/or species, there being no allowable generic or linking claim.

4. Claims 1, 12, 72, 74, 77-79, 81, 95 and 97, drawn to a peptide, a pharmaceutical composition comprising the peptide thereof, comprising an amino acid sequence X-Y or Y-X, are under consideration in the instant application.

5. Applicant's election of "2 amino acids" and "synthetic" as the species for the "Number of amino acid residues" and "Y amino acid" respectively, is acknowledged.

Sequence Compliance

6. The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825. The sequences in Figures 1, 3a, 3c, 8a, 8b, 10b, 11, 16a, 16b, 19a, 20a, 23, 42c, 46a, 46b are not associated with a relevant sequence identifier.

Appropriate correction is required.

Specification

7. The disclosure is objected to because of the following informalities:

A) Internet address:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, page 44, line 17). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required

B) Brief description of Drawings

The brief description of the drawings is objected because sequence identifiers for the following sequences are missing: Figures 3C, 12, 13, 17, 18, 21, 22, 41, 44a and b, etc. Appropriate correction is required.

The brief description of the drawings to Figure 39 is objected because Figure 39 has 5 peptides and the brief description has four sequence identifiers (i.e. SEQ ID NOs: 46-49).

C) Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested:

PEPTIDES AND METHODS USING SAME FOR DIAGNOSIS AND TREATMENT OF AMYLOID-ASSOCIATED DISEASE

Appropriate correction is required.

Claim Objections

8. Claims 12, 72, 74, 77-79, 81and 95 are objected to because of the following informalities:

a) Claims 12 and 81 recite non-elected inventions (i.e. non-elected sequences).

b) Claim 72 is canceled per amendment dated 12/30/2005 (41-73 cancelled), however, Applicants have responded to the restriction requirement, stating the election of claim 72 and its dependent claims. It is unclear if this is a typo. Appropriate correction is required.

c) Claims 74, 77-79, 81and 95 are objected because of depending from an objected claim.

Claim Rejections
35 USC § 101 – Non-statutory subject matter

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 1, 12, 72, 74, 77-79, 81and 95 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed peptide is not "isolated" or "synthesized". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v.

Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated", or "synthesized" as taught on para 0150 of the instant specification. See MPEP 2105.

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 12, 72, 74, 77-79, 81and 95, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 72 is rejected for being vague and unclear because of the limitation "A pharmaceutical composition .....comprising....a peptide including....X-Y or Y-X". It is not ascertainable as to whether the pharmaceutical composition comprises a peptide **and** includes the amino acid sequence X-Y or Y-X; or the peptide itself includes (meaning comprises) the amino acid sequence X-Y or Y-X.

12. Claims 1, 72, are rejected under 35 U.S.C. 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The claims recite "a peptide" meaning "any peptide". The specification teaches that the term "peptide" encompasses native peptides (degradation products, synthetic or recombinant peptides) (para 0150).

It is not clear which of the above peptides represent the claimed invention. Appropriate clarification and correction is needed.

13. Claims 12, 74, 77-79, 81 and 95 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 72, 74, 77-79, 81, 95 and 97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the claimed synthetic peptides, for the inhibition of amyloid fibril formation in the presence of pancreatic islet amyloid polypeptide (IAPP) in vitro, does not reasonably provide enablement for a pharmaceutical composition comprising the claimed peptides for use in the treatment or prevention of any amyloid associated disease in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

15. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art,

the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

16. The claims are drawn to a pharmaceutical composition comprising the peptide thereof, comprising an amino acid sequence X-Y or Y-X, wherein the peptide is 2-15 amino acids in length, 'X' is an aromatic amino acid, and 'Y' is any amino acid other than glycine. The claims further recite that 'Y' is a synthetic Cα-methylated amino acid or α-aminoisobutyric acid (Aib), and is a β-sheet breaker amino acid.

17. The specification teaches that synthetic peptides function as β-sheet breakers to disrupt the β-pleated sheets and inhibit the formation of amyloid fibrils in a rat brain model of amyloidosis (page 3, lines 11-18). The specification also teaches that synthetic amino acids like Aib are β-sheet breaker amino acid, that when substituted in the peptide, allows the peptide to bind to amyloid polypeptides, without forming aggregation thereof (page 25, lines 20-29). The specification further teaches that in order to prevent the proteolytic degradation of short therapeutic peptides by cellular proteases, the peptides have D-stereoisomers of the natural amino acids (page 35, lines 24-28). Using transmission electron microscopy, it was observed that Aib containing peptides do not form fibrillar structures when incubated with IAPP peptides (Example 41). Additionally, using a fluorescence assay, the specification demonstrates that the

Aib-modified peptides inhibit the assembly of full length IAPP (Example 44; Figure 47). Furthermore, Example 45 demonstrates that di-aromatic peptides like EG16 or D-Tyr-Aib (SEQ ID NO: 121) inhibit the aggregation of IAPP peptides (Figure 48; Table 7). However, the specification does not disclose any methods or working examples for extrapolating the in vitro data showing the effect of the claimed peptides on reduced aggregation of fibrils to treating or preventing, meaning stopping any amyloid associated disease in an individual. Undue experimentation would be required by one skilled in the art to achieve predictability and success.

18. Relevant literature teaches that short synthetic peptides can function as β-sheet breaker and inhibit the aggregation of amyloid fibrils in vitro. For example, Soto et al. (Nature Med 4: 822-826, 1998) teach that the five amino acid residue (LPFFD or iAβ5) resulting from the substitution of hydrophobic region of the N-terminal region of Aβ peptide, is a β-sheet breaker that disassembles preformed fibrils in vitro (abstract; page 822, para 2; Figure 1). Soto et al. further demonstrate that iAβ5 injected in rats results in the inhibition of cerebral amyloid deposition (Figure 4; page 823, col 1, para 2). Using combinatorial pentapeptide libraries, Tjernberg et al. (JBC 272, 12601-12605, 1997) teach that the ligands composed of D-amino acids increase the bioavailability and inhibit the formation of amyloid fibrils (abstract). However, Soto's rat model is more like a screening model for "efficient and quick" selection of Aβ inhibitors (Soto et al, page 823, col 2, para 4), therefore, findings in this model cannot be predictably extrapolated to

treating or preventing amyloid associated diseases like AD. There is no support in the art to show therapeutic or preventive actions by using the claimed synthetic peptides on transgenic animal models that resemble widespread amyloidosis as observed in AD. Undue experimentation would thus be required of skilled practitioner to achieve success in treatment, even more prevention.

19. Amyloid associated disorders is broadly referred to several progressive diseases that result from varied etiologies, e.g. genetic, metabolic or other unknown factors like chronic infection or inflammation, predominantly eliciting abnormal deposits of amyloid protein. Because of the well-known complexities in the pathophysiology of the various amyloid associated diseases such as Alzheimer's Disease (AD), it is unpredictable to decipher preventive measures in vivo. In fact Soto et al.'s statement that "The inhibition of in vivo Aβ deposition may follow the same mechanism, but because of the higher complexity of the system we can not rule out other possibilities" (page 823, col 2, para 3), proves that several mechanisms are involved in these diseases. Therefore, while the synthetic peptides inhibit amyloid aggregation in vitro, it is neither known in the art nor is it supported in the specification, that the claimed pharmaceutical composition can be used in the in vivo treatment or prevention of amyloid associated diseases. The claims as instantly presented constitute an invitation to experiment using the peptides for the prevention or treating of such diseases.

20. It is further noted that the term "preventing" corresponds to stopping of disease, and the term "pharmaceutical" determines an intended use of the

claimed peptide. The fact that there is a significant progression in the pathology at the time of diagnosis of most of the amyloid aggregation related diseases, for example AD, indicates a dearth in the understanding of the etiology of such complex diseases. Furthermore, prevention can only be achieved with a reasonable success, if "the pathology is understood and there is evidence that manipulation of that pathology leads to clinical benefit", which poses a sure challenge for diseases like AD (Sano, Curr Neurol Neurosc Rep 2: 392-399, 2002; abstract). Additionally, it is imperative that studies involving the prophylactic intervention of such complicated and chronic diseases should be conducted on art established non-human models to prove the predictability and success. Neither the instant specification nor the available art provides or suggests such working protocols. The instant specification neither provides enough guidance for such prophylactic use of the peptides, nor demonstrates the same through working examples to establish successful use of the claimed product, thus, requiring undue experimentation on part of one skilled in the art to discover how to practice the claimed invention.

21. As the molecular processes of pathogenesis of amyloid associated disease are yet to be fully uncovered, and as the amyloid associated diseases are largely recalcitrant to treatment, the success of treatment and/or prevention would be unpredictable, thus the invention would entail undue experimentation and substantial inventive contribution for the skilled artisan to discover how to use Applicant's invention as currently claimed.

22. Due to the large quantity of experimentation necessary to use the pharmaceutical composition comprising the claimed peptides for the prevention or treatment of amyloid associated diseases; lack of direction/guidance presented in the specification regarding the same; the absence of animal models or relevant working examples demonstrating the same; the complex nature of the invention; the state of the prior and post art which has yet to determine causative features of such diseases; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Double Patenting

Non-Statutory-Provisional

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

24. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

25. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

26. Claims 1, 12, 72, 74, 77-79, 95 and 97 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 9-10 of copending Application No. 11/471,657, filed 21 June 2006. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a peptide or a pharmaceutical composition comprising a peptide comprising amino acid sequence X-Y or Y-X, the peptide being 2 to 15 amino acids in length.

(I) The only difference between the claims of the '657 application and the claims of the instant application is that claims 1 and 2 of the '657 application recite a peptide as set forth in SEQ ID NO: 145, while claim 12 of the '852 application recites a genus of peptide sequences selected from a group consisting of sequences, for example SEQ ID NO: 145. **(II)** The only difference between claims 3 and 4 of the '657 application and the instant claims are that while the claims of the '852 application broadly recite a pharmaceutical composition comprising a peptide having 2-15 amino acids in length, having the sequence X-Y, and a pharmaceutically acceptable carrier or diluent, wherein X is an aromatic amino acid and Y is an amino acid other than glycine, and is a β-sheet breaker amino acid; the claims of the '657 application recite SEQ ID NO: 145 that represents a species of the genus claims of application '852. The limitations of X and Y amino acids as set forth in the claims of the '657 application are inherent

because the specification of the '657 application teaches that the X residue is an aromatic amino acid (page 5; lines 21-29, 34; page 6, line 1), and the Y residue can be α-aminoisobutyric acid (Aib), which forms the β-sheet breaker (page 7, lines 30-33). Furthermore, the specification of '852 also teaches that the peptide EG30 or SEQ ID NO: 145 is represented by D-Trp-Aib (page 86, Table 7). Additionally, claims 1, 2 and 4 of the '657 application recite cyclic or linear forms of the peptide, while the claims of the instant application do not recite such forms of the peptide. This limitation is also inherently disclosed in the '852 application, which teaches that the peptides of the invention can be synthesized in linear or cyclic forms (page 6, lines 25-26).

27. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

28. Claims 1, 72, 74, and 77-79, are rejected under 35 U.S.C. 102(b) as anticipated by Pispisa et al., Biopolymers 53: 169-181, 2000.

29. The claims recite a peptide, or a pharmaceutical composition comprising the peptide thereof, comprising an amino acid sequence X-Y or Y-X, wherein the peptide is 2-15 amino acids in length, 'X' is an aromatic amino acid, and 'Y' is any amino acid other than glycine, is a synthetic Cα-methylated amino acid or α-aminoisobutyric acid (Aib), and is a β-sheet breaker amino acid.

30. Pispisa et al. teach linear Aib based hexapeptides comprising the "Trp-Aib' sequence (Abstract; page 170, col 1, para 3; page 172, Table 1), thus meting the claimed requirement of 2-15 amino acids, wherein 'X' is an aromatic amino acid and 'Y' is Aib. Although the reference does not specifically teach "a pharmaceutical composition for treating or preventing an amyloid-associated disease", this limitation present in the preamble merely provides an intended use of the claimed invention, which does not add patentability to the claimed product. As stated in the MPEP, ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation") *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997). Thus Pispisa et al. anticipates the claimed invention.

Conclusion

31. No claims are allowed.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
15 November 2008

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649